REMARKS

1. Preliminary Matters

a. Status of the Claims

Claims 21, 23-25, 27, 28, 35, and 36 are pending in this application. Claims 24, 25, 27, and 28 are hereby canceled without prejudice to pursuing the claimed subject matter in a continuing application. Claims 21, 23, and 36 are amended wherein claim 23 is now in independent form. New claims 38 and 39 are added. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the application. Upon entry of these amendments, claims 21, 23, 35, 36, 38, and 39 will be pending and under active consideration.

b. Amendments to the Claims

Support for the amended and new claims can be found in the application as originally filed as shown in Table A.

Table A

Claim	Support
38	claims 12-14
39	claims 12-14

c. Priority

On page 2 of the Office Action, the Examiner alleges that priority U.S. Prov. App. No. 60/441,241 fails to disclose any of the presently claimed SEQ ID NOs:128, 131, 133, 477, 480, and 482, and therefore fails to provide adequate support or enablement for the present claims. The applicant respectfully submits that each of SEQ ID NOs:128, 131, 133, 477, 480, and 482 is disclosed in the sequence listing for U.S. Prov. App. No. 60/441,241 with the same SEQ ID number. The applicant submits herewith the cover sheet, filed with priority application 60/441,241 on January 17, 2003, wherein receipt of the CDs for the priority application was acknowledged as received by the USPTO. One of the CDs discloses the sequence listing. Accordingly, the priority of the sequences set forth in SEQ ID NOS: 128, 131, 133, 477, 480, and 482 is the filing date of U.S. Provisional Application No. 60/441,241 (January 17, 2003).

2. Patentability Remarks

a. 35 U.S.C. § 101

On pages 3-6 of the Office Action, the Examiner rejects claims 21, 23-25, 27, 28, 35, and, 36 under 35 U.S.C. § 101 because the claimed subject matter allegedly is not supported by either a specific and substantial asserted utility, a well established utility.

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See In re Fisher* 421 F.3d at 1371 and Guidelines. Applicant respectfully submits that the application provides a specific utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and the Guidelines.

In *Fisher*, the claims at issue were directed to five (5) out of more than 32,000 EST that were disclosed in the application. Each of disclosed ESTs was from a cDNA library from pooled leaf tissue of a maize plant. The Fisher application did not disclose the location of the ESTs in the genome or the function of the underlying genes. Fisher asserted that the utilities for claimed ESTs were (1) serving as a molecular marker; (2) measuring the level of mRNA in a tissue sample; (3) provide a source of primers for PCR of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *See Id.* at 1367 and 1368. It is important to note that each of the utilities asserted were not limited to any specific gene, genetic location or protein.

The *Fisher* court concluded that the asserted utilities were clearly not "specific." The court explained that any EST transcribed from any gene in maize could perform the seven uses such as being a molecular marker, a primer, or measure the level of RNA in a tissue sample. In other words, nothing about the seven alleged uses separated the claimed ESTs from the vast number of other ESTs also disclosed in the application. The keystone to the lack of specific utility in *Fisher* is that the claimed ESTs **did not correlate to an underlying gene of known function found in the maize genome**.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids maybe used to target and modulate expression of **specific** gene

transcripts. Table 2, lines 7203-7207, 7383-7387, and 7428-7432, of the specification disclose that the **claimed microRNA-related sequences specifically target** mRNA transcripts of (1) ACADSB (targeted by SEQ ID NO:477), (2) ZNF36 (targeted by SEQ ID NO:482), or (3) INHBA (targeted by SEQ ID NO:480).

Consequently, the claimed nucleic acids are of a **specific and unique nature** because these nucleic acids regulate the translation of specific mRNAs from **three corresponding target genes: INHBA, ZNF36, and ACADSB**. Accordingly, the asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating these targets.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public. *See In re Fisher* at 1371 and the Guidelines. Applicant respectfully submits that the application provides a substantial utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and the Guidelines.

In Fisher, it was admitted that the underlying genes for the ESTs had no known function. Fisher argued this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, Fisher failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Id.* at 1373 quoting *Brenner v. Manson*, 383 U.S. 519 (1966).

In further sharp contrast to *Fisher*, the present application discloses that the claimed nucleic acids may be used to bind and regulate mRNA transcripts of INHBA, ZNF36, or ACADSB. *See* Table 2, lines 7383-7387 (INHBA), Table 2, lines 7428-7432 (ZNF36), and Table 2, lines 7203-7207 (ACADSB).

(a) ACADSB

At the time of filing, it was known prior to the filing of the present application that ACADSB was a member of the acyl-CoA dehydrogenase family of mitochondrial enzymes. ACADSB was also known to react with 2-methylbranched chain substrates and with short straight chain acyl-CoAs. *See* Rozen *et al.*, Genomics, 24, 280-287 (1994). It was also known

that metabolism of 2-methylbranched chain fats in humans was postulated to occur in peroxisomes because of accumulation of branched chain fatty acids in patients with inherited deficiencies of peroxisomes. *See* Rozen *et al.*, Genomics, 24, 280-287 (1994).

(b) INHBA

With respect to INHBA, it was known prior to the filing of the present application that INHBA encodes activin βA, which may associate with activin βB (encoded by the INHBB gene). These activins were known to associate to form activin AB heterodimers or homodimers. Furthermore, it had been previously shown that mice with a homozygous null mutation in the INHBA locus failed to suckle and have disruption of whisker palate, and tooth development, and die shortly after birth. *See* Brown *et al.*, Medical Endocrinology, 17(12): 2404-2417 (December, 2003).

(c) ZNF36

Lastly, with respect to ZNF36, Tommerup and Vissing identified ZNF36, which they called ZNF139. The ZNF36 cDNA predicted a protein belonging to the Kruppel family of zinc finger proteins. *See* Database OMIM, Entry No. 601260, and Tommerup and Vissing, Genomics, 27(2):259-264 (May 1995).

The evidence described above clearly supports that the claimed nucleic acids have a number of presently available benefit to the public, including: (1) as a diagnostic of developmental disorders in mice; (2) modulating expression of any of ACADSB, INHBA, and/or ZNF36; or (3) indirectly modulating expression of genes downstream of ZNF36. In view of the application providing particular targets of known function for the claimed microRNA-related nucleic acids, Applicant respectfully submits that the specific and substantial utility requirements are satisfied in accordance of Fisher and the Guidelines.

(3) Credible Utility

An asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided. An assertion is credible unless (i) the logic underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Accordingly, the invention must be operable to achieve useful results. *See Guidelines* at page 5 and *In re Swartz*, 232 F.3d 862 (Fed. Cir. 2000). The proper inquiry for determining credible utility is whether a person of ordinary skill in the art would conclude that the asserted utility is more likely than not

true. Applicant respectfully submits that the record clearly shows that one of ordinary skill in the art would believe that the claimed nucleic acids may be used to modulate expression of the specific mRNA targets.

Furthermore, Dr. Yitzhak Pilpel, who is an expert in the field of microRNA and RNAi biology, states in the attached declaration (Appendix A) that the claimed nucleic acids (SEQ ID NOs: 477, 480, and 482) would likely inhibit expression of the ACADSB mRNA transcript (Table A, page 7, column B, row 2), INHBA mRNA transcript (Table A, page 6, column B, row 1), and ZNF36 mRNA transcript (Table A, page 6, column B, row 2), respectively. Dr. Pilpel's opinion is based upon a number of facts.

(a) Characteristics of microRNA-target mRNA binding

Dr. Pilpel states that researchers in the microRNA field believed that there are a number of characteristics of inhibition of protein expression via target mRNA interference by an endogenous or synthetic nucleic acid of 18-25 nucleotides in length, such as a microRNA. For example, the 5' end of the microRNA may contain a "seed" that is full complementary between the first 1-8 base pairs of the 5' of the microRNA and the target mRNA. *See* paragraphs 2 and 3, Pilpel Declaration. This seed may be conserved and is often flanked by adenosine. *See* paragraph 3, Pilpel Declaration. If there is insufficient base-pairing of the microRNA 5' seed there may be compensatory complementation at the 3' end of a microRNA and its target mRNA sequence. *See* paragraph 3, Pilpel Declaration. Finally, although not obligatory, there may be multiple binding sites for a microRNA on a mRNA target, which may enhance the binding effect of target repression. *See* paragraph 3, Pilpel Declaration.

Importantly, Dr. Pilpel states that the claimed nucleic acid sequences, set forth as SEQ ID NOs:477, 480, and 482, and their target sequences are consistent with the characteristics of the microRNA:target mRNA binding described herein. *See* paragraph 6, Pilpel Declaration. In view of these conserved characteristics, and Table A of his Declaration, Dr. Pilpel concludes that the microRNA of SEQ ID NO:477 is likely to inhibit expression of ACADSB protein (page 7, column B, row 2, of Table A), the microRNA of SEQ ID NO:480 is likely to inhibit expression of INHBA protein (page 6, column B, row 1, of Table A), and the microRNA of SEQ ID NO:482 is likely to inhibit expression of ZNF36 protein (page 6, column B, row 2 of Table A). *See* paragraph 6, Pilpel Declaration.

(b) MicroRNA algorithms

Dr. Pilpel states that several effective microRNA:target algorithms have been based upon the characteristics of microRNA:target mRNA binding described above. *See* paragraph 4, Pilpel Declaration. Dr. Pilpel provides TargetScan (developed by Lewis *et al., Cell* 115:787-798 (2003)) and miRanda (developed by Enright *et al.*, *Genome Biology* 5:R1 (2003)) as examples of such algorithms. The TargetScan algorithm predicted 15 targets of various miRNAs identified by Lewis, and 11 of the predicted interactions between a particular miRNA and target mRNA were biologically validated with a false positive rate between 22 and 31%. The miRanda algorithm was also an effective microRNA:target algorithm, where 9 out of 10 predicted targets identified by the miRanda algorithm in Enright were biologically validated with a 24-39% false positive rate. *See* paragraph 4, Pilpel Declaration.

Importantly, Dr. Pilpel states that each of SEQ ID NO:477, 480, and 482 and their respective targets are consistent with microRNA and target mRNAs predicted by the algorithms described above. *See* paragraphs 4 and 5, Pilpel Declaration. Moreover, Dr. Pilpel states that the TargetScan algorithm detects the binding of each claimed nucleic acid. *See* paragraph 5, Pilpel Declaration and page 7, column B, row 2 (ACADSB); page 6, column B, row 1 (INHBA); and page 6, column B, row 2 (ZHF36) of Table A. In view of these facts, Dr. Pilpel concludes that the microRNA of each claimed nucleic acid is likely to inhibit expression of the protein where co-expressed. *See* paragraph 6, Pilpel Declaration.

(c) ACADSB, INHBA, and ZHF36 are Credible Targets

Applicant submits that each of ACADSB, INHBA and ZHF36 is a credible target for trans-acting regulatory elements.

(a) ACADSB

The Pilpel Declaration indicates that a nucleic acid having the sequence as set forth in SEQ ID NO:477 has been biologically validated. See Row 2, page 7, Table A. Accordingly, ACADSB is an important target in nature for trans-acting elements such as microRNAs. Furthermore, the claimed nucleic acids are capable of binding ACADSB with 20 out of 22 nucleotides of complementarity, as demonstrated in Table 2, lines 7203-7207 of the specification, and as shown below.

```
Nucleic-acid SEQ ID NO:477

            __    C  TA
5′ GCCTTTATT  TCCA AT  GATGG 3′
3′ CGGAAATAA  AGGT TA  CTACC 5′
          AA    T  __

Target gene : ACADSB
20/22 complementary base pairs
```

In view of the foregoing, Applicant asserts that a person of ordinary skill in the art would more than likely conclude that the claimed nucleic acids may be used to modulate expression of ACADSB, which in turn would modify the accumulation of 2-methylbranched chain substrates.

(b) INHBA

The Pilpel Declaration indicates that a nucleic acid having the sequence as set forth in SEQ ID NO:480 has been biologically validated. See Row 1, page 6, Table A. Accordingly, INHBA is an important target in nature for trans-acting elements such as microRNAs. Furthermore, the claimed nucleic acids are capable of binding INHBA with 20 out of 22 nucleotides of complementarity, as demonstrated in Table 2, lines 7383-7387 of the specification, and as shown below.

```
Nucleic-acid SEQ ID NO:480

           C      CA___
5′ TGCTATTT GGCTGC     GAGTGT 3′
3′ ACGATAAA CCGACG     TTCACA 5′
   _       CCGAC

Target gene : INHBA
20/22 complementary base pairs
```

In view of the foregoing, Applicant asserts that a person of ordinary skill in the art would more than likely conclude that the claimed nucleic acids may be used to modulate expression of INHBA, which in turn would modify, for example, mouse palate and/or tooth development.

(c) ZHF36

The Pilpel Declaration indicates that a nucleic acid having the sequence as set forth in SEQ ID NO:482 has been biologically validated. See Row 2, page 6, Table A. Accordingly, ZHF36 is an important target in nature for trans-acting elements such as microRNAs. Furthermore, the claimed nucleic acids are capable of binding ZHF36 with 16 out of 22

nucleotides of complementarity, as demonstrated in Table 2, lines 7428-7432 of the specification, and as shown below.

```
Nucleic-acid SEQ ID NO:482

           C  C
5′ TCTATGTT CT GTTTCC 3′
3′ AGATACAA GA CAAAGG 5′
           A  _

Target gene : ZNF36
16/22 complementary base pairs
```

In view of the foregoing, Applicant asserts that a person of ordinary skill in the art would more than likely conclude that the claimed nucleic acids may be used to modulate expression of ZHF36, which in turn would modify, for example, downstream transcription.

In summary, Applicant respectfully submits that a proper credible utility is asserted for the claimed nucleic acids. Applicant respectfully asserts that a specific and substantial utility has been demonstrated both in the specification and by what was recognized as well as established in the art at the time of filing, and the utility is credible. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 101.

b. 35 U.S.C. §112, first paragraph –Enablement

On page 6 of the Office Action, the Examiner asserts that because the claimed subject matter lacks substantial utility, the specification also does not provide an enabling disclosure. Applicant disagrees. In view of the claimed subject matter having credible, specific and substantial utility as described above, Applicant submits that the specification enables the claimed subject matter and respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph.

c. 35 U.S.C. § 112, first paragraph—Written Description

On page 6 of the Office Action, the Examiner rejects claims 21, 23-25, 27, 28, 35, and 36 as allegedly failing to comply with the written description requirement. Specifically, the Examiner states that there is a lack of adequate written description support for the claimed limitation of "at least 83.3%" and the nucleic acid length limitation of between "20 to 120." Amended claim 21 no longer recites the limitations of "at least 83.3%" or "20 to 120." Claims 24 and 28 are canceled, thereby rendering moot the rejection of these claims. Accordingly,

Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 21, 23-25, 27, 28, 35, and 36 under 35 U.S.C. § 112, first paragraph.

d. 35 U.S.C. § 102(e)

(1) In view of WO 2005/001128 A2 ("Moyer")

On page 7 of the Office Action, the Examiner rejects claims 21 and 25 under 35 U.S.C. § 102(b) as allegedly being anticipated by Moyer. Claim 25 is canceled, thereby rendering moot the rejection of this claim.

With respect to claim 21, Applicant respectfully submits that the present application claims the benefit of the filing date of U.S. Prov. App. No. 60/441,241, which was filed on January 17, 2003. *See* originally filed provisional application cover sheet submitted herewith. U.S. Prov. App. No. 60/441,241 properly disclosed SEQ ID NO:131 in the CDs as originally filed, and acknowledged by the USPTO, on January 17, 2003. *See* originally filed provisional application cover sheet submitted herewith. In view of the Applicant's claimed priority date and the disclosure of SEQ ID NO:131 in U.S. Prov. App. No. 60/441,241, Applicant respectfully submits that the present application described the claimed nucleic acid SEQ ID NO:131 prior to the earliest Moyer priority application (U.S. provisional application 60/462,204 filed on April 11, 2003). In view of the foregoing remarks, Applicant requests that the Examiner reconsider and withdraw the rejection of claims 21 and 25 under 35 U.S.C § 102(e) in view of Moyer.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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Dated: April 21, 2008

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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☐ *Additional inventors are being named on the ___separately numbered sheets attached hereto.*

TITLE OF THE INVENTION (280 characters max)

BIOINFORMATICALLY DETECTABLE GROUP OF NOVEL VACCINIA REGULATORY GENES AND USES THEREOF

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ENCLOSED APPLICATION PARTS *(check all that apply)*

- [X] Specification — *Number of Pages* 117
- [X] CD(s), Number 5 mj.
- [X] Drawing(s) — *Number of sheets* 34
- ☐ Other (specify)
- ☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)

- [X] Applicant claims small entity status. See 37 CFR 1.27.
- [X] A check or money order is enclosed to cover the filing fees
- [X] The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 01-0035
- ☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE AMOUNT ($) $80.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- [X] No.
- ☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE Jay S. Cinamon

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Date January 17, 2003

REGISTRATION NO. *(if appropriate)* 24,156

Docket Number: 206,045

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This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C., 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C., 20231.

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